

Remarks

Reconsideration of this Application is respectfully requested.

Claims 146-148, 150-174, 176, 177, 180-203, 233 and 237-244 are pending in the application, with claims 146-148, 176, 177, and 233 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. *The Rejections*

A. *Legal Principles of Anticipation*

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 361 (Fed. Cir. 1987)). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). If the prior art does not necessarily function in accordance with, or does not include, the claimed limitations, it does not anticipate. *Mehl/Biophile International Corp. v. Milgram*, 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999).

B. First Rejection Under 35 U.S.C. § 102(b)

Claims 146, 150, 168-169, 233, 241, and 242 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Motohashi, *West Australian Nut and Tree Crops Association* 16:48-59, West Australian Nut and Tree Crops Association, Australia (1991) ("Motohashi") in view of Hunder *et al.*, *Arthritis & Rheumatism* 17(6):955-963 (1974) ("Hunder"). Applicants respectfully traverse this rejection.

I. Declaration by Sunyoung Kim Under 37 C.F.R. § 1.132

The Applicants' direct the Examiner to the Declaration of Sunyoung Kim, D. Phil., under 37 C.F.R. § 1.132 filed concurrently with the Reply. In the Declaration, Dr. Kim explains in detail why one of ordinary skill in the art at the time this application was filed would not have understood Motohashi combined with Hunder to teach the treatment of rheumatoid arthritis by reducing IgE production in a mammal in need thereof. Based upon the arguments disclosed in the Declaration of Dr. Kim and those listed below, it is respectfully requested that the rejection of pending claims 146, 150, 168-169, 233, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

2. The Pending Claims Are Not Expressly or Inherently Anticipated by Motohashi

The Examiner asserts:

Motohashi teaches the use of *Actinidia arguta* in treatment of . . . rheumatoid arthritis. It is taken orally (see pages 48-49) . . . Hunder et al. is solely used to show that there is an increase in IgE in patients with rheumatoid arthritis. Hence, treatment of rheumatoid arthritis would result in the decrease of IgE in patients with rheumatoid arthritis.

See Office Action at pages 5-6. Applicants respectfully disagree.

The present claims are not anticipated by Motohashi because the reference does not disclose reducing IgE production in a mammal in need thereof by orally administering an extract of *Actinidia arguta*. First, Motohashi does not expressly mention reducing IgE production in a mammal in need thereof. The reference also does not indicate that by treating humans afflicted with any of the listed indications with an extract of *Actinidia arguta*, IgE production would be reduced in humans in need thereof. In fact, the reference does not mention any relationship between IgE production and the treatment of any indication. Therefore, the reference does not teach that the afflicted humans were in need of a reduction in IgE production. Thus, Motohashi does not expressly anticipate the present claims.

Moreover, Motohashi does not inherently describe reducing IgE production in a mammal in need thereof. The Examiner has not established that the reference necessarily includes the claimed limitation "wherein said [*Actinidia arguta*] extract is provided in an amount sufficient to reduce IgE production in said mammal." The Examiner has not shown that an oral extract of *Actinidia arguta* administered to humans for the treatment of any of the listed indications would *necessarily reduce IgE production in said mammal*. While the Examiner has attempted to establish a relationship between IgE production and rheumatoid arthritis ("RA") by referencing Hunder, the Examiner did not acknowledge the statement in Hunder that "*[n]o significant correlation was found between serum IgE concentration and the severity of RA*" nor was evidence found of the local production of IgE in synovial fluid in RA." See abstract of Hunder at page 955 (emphasis added). This statement alone indicates that the treatment of rheumatoid arthritis may not necessarily result in the reduction of IgE

production. To elaborate further, one of ordinary skill in the art would appreciate that treatment of RA would necessarily reduce the severity of RA. However, the aforementioned quote from Hunder teaches that such a reduction in the severity of RA resulting from RA therapy would not correlate with a change in serum IgE concentration. Therefore, Hunder does not teach that treatment of rheumatoid arthritis would result in the decrease of IgE in patients with rheumatoid arthritis as claimed by the Examiner.

As noted in Dr. Kim's Declaration (submitted concurrently herewith), a result or an association is considered statistically significant by universally accepted statistical standards of evaluating scientific data if the result or association is unlikely to have occurred by chance. Hunder clearly states in the abstract that "no significant correlation was found between serum IgE concentration and severity of RA." *See abstract of Hunder at page 955.* A scientist of ordinary skill in the art would interpret, based on scientifically acceptable statistical standards, the statement "no significant correlation" to mean that there was no statistically significant correlation between serum IgE concentration and severity of RA and that any variations of serum IgE concentration seen in patients with varying degrees of RA symptoms occurred by chance alone.

As further noted in Dr. Kim's Declaration, "Quantitative Techniques," *NIST/SEMATECH e-Handbook of Statistical Methods.*: Sections 1.3.5 – 1.3.5.3, National Institute of Standards and Technology - U.S. Commerce Department (2010) (enclosed herein as Exhibit B) ("NIST") supports this interpretation and defines the "hypothesis test," which includes the two-sample *t*-Test statistical approach used by Hunder, as follows:

[A] hypothesis test attempts to refute a specific claim about a population parameter based on the sample data...To reject a

hypothesis is to conclude that it is false. However, to accept a hypothesis does not mean that it is true, only that we do not have evidence to believe otherwise. This hypothesis tests are usually stated in terms of both a condition that is *doubted (null hypothesis)* and a condition that is *believed (alternative hypothesis)*... Statistical significance simply means that we reject the null hypothesis.

See NIST at Section 1.3.5, page 245 (emphasis added).

Therefore, Hunder in view of NIST implies a null (doubted) hypothesis that variations of serum IgE concentration seen in patients with varying degrees of RA symptoms occurred by chance alone and implies an alternative (believed) hypothesis that a correlation between serum IgE concentration and severity of RA exists. Given that Hunder found no significant correlation between serum IgE concentration and the severity of RA and based upon the teachings of NIST, the alternative (believed) hypothesis is rejected, and the null (doubted) hypothesis of "variations of serum IgE concentration seen in patients with varying degrees of RA symptoms occurred by chance alone" must be accepted.

Therefore, the statement in Hunder that "[n]o significant correlation was found between serum IgE concentration and the severity of RA" should be considered as "it has occurred by chance" and as implying that *no correlation* in fact existed between serum IgE concentration and the severity of RA. *See abstract of Hunder at page 955. Aihara, Y., Jahromi, B., Yassari, R., Savama, T., and Macdonald, R. Neurosurgery 52: 661-667 (2003) (enclosed herein as Exhibit C) ("Aihara") supports this notion in the following statement:*

There was *no significant correlation* between arterial cGMP contents and the severity of vasospasm. Conclusion: DETA/NO did not prevent vasospasm. There was *no correlation* between the severity of vasospasm and cyclic adenosine monophosphate and cGMP levels in the cerebral arteries.

See Airhara abstract (emphasis added).

As further noted in Dr. Kim's Declaration, the statement in Hunder that "[n]o significant correlation was found between serum IgE concentration and the severity of RA" should be further considered as "the severity of RA **does not depend on** the serum IgE concentration." *See* abstract of Hunder at page 955. Nguyenkim, J. and DeAngelis, G. *The Journal of Neuroscience* 23: 7117-7128 (2003) (enclosed herein as Exhibit D1) ("Nguyenkim") supports this notion in the following statement:

We find **no significant correlation** between these variables ($r = 0.02$; $p = 0.89$), indicating that tilt tuning **does not depend on** asymmetric surround effects.

See Nguyenkim at page 7126, lines 29-31 (emphasis added).

As further noted in Dr. Kim's Declaration, the statement in Hunder that "[n]o significant correlation was found between serum IgE concentration and the severity of RA" should be further considered as "serum IgE concentration had **no association** with the severity of RA." *See* abstract of Hunder at page 955. Halawaty, S., ElKattan, E., Azab, H., ElGhamry, N., and Al-Inany, H. *J. Obstet. Gynaecol. Can.* 32: 687-690 (2010) (enclosed herein as Exhibit D2) ("Halawaty") support this notion in the following statement:

There was **no significant difference** between the two groups in mean age, levels of serum AMH, serum FSH, FBG, 2 hr PP, or AFC. Ovarian volume was significantly lower in obese women (3.7 ± 0.8 ml) than in non-obese women (6.6 ± 0.4 ml) ($P = 0.03$). There was **no significant correlation** between BMI and serum AMH, serum FSH, FBS, or 2 hr PP. Conclusion: Obesity has **no association** with levels of serum FSH, AMH, blood glucose, or AFC indicating that obesity is unlikely to affect ovarian reserve in the perimenopausal age group.

See Halawaty abstract at page 687 (emphasis added).

In summary, the statement in Hunder that "*no significant correlation*" was found between serum IgE concentration and the severity of RA" should be interpreted to mean the following: (a) there was **no correlation** between serum IgE concentration and the severity of RA, (b) the severity of RA **does not depend on** serum IgE concentration, and (c) the severity of RA has **no association** with serum IgE concentration.

Hunder further states in the abstract that "[s]erum and synovial fluid levels of immunoglobulin E (IgE) were significantly increased in patients with rheumatoid arthritis (RA) but were normal in degenerative arthritis (DJD)... [T]he increased IgE in RA may be the result of a general immune response seen in this disease." As noted in Dr. Kim's Declaration, this statement by Hunder refers to the increased levels of IgE in RA patients compared to degenerative arthritis (DJD) patients rather than the comparison of serum IgE levels among patients with varying degrees of severity of RA. Dr. Kim's Declaration further notes that Table 1 of Hunder only indicates a significant increase in serum IgE concentrations between patients with RA and DJD. While Table 1 also provides values for serum IgE concentrations in normal patients, Hunder does not report in Table 1 a significant increase in serum IgE concentrations between RA patients and normal patients. Table 1 of Hunder further indicates that the values for serum IgE concentrations in normal patients were derived from a previously published study. As stated in Dr. Kim's Declaration, a statistical comparison of serum IgE levels between normal patients and RA patients may have been omitted by Hunder, because the comparison of values between two studies often prevents the establishment of a valid statistical correlation due to differences in experimental techniques, experimental conditions, control groups, and other potential variables between

the two studies. For the reasons mentioned above, the teachings of Hunder do not exclude the likely possibility that the lower serum IgE levels in DJD patients compared to RA patients were the result of or caused by the DJD disease state. Therefore, one of ordinary skill in the art would at most interpret the data disclosed in Table 1 of Hunder to suggest a statistical difference or correlation between serum IgE levels and different types of arthritic disease (*i.e.*, RA and DJD) and would not erroneously interpret the data disclosed in Table 1 to suggest a statistical correlation between serum IgE levels of healthy patients and RA patients. As noted above and in Dr. Kim's Declaration, the absence of a statistically significant correlation concedes the null hypothesis of no correlation.

The statement "the increased IgE in RA may be the result of a general immune response seen in this disease" as it relates to a comparison between RA patients and DJD patients further refutes the Examiner's claim that "treatment of rheumatoid arthritis would result in the decrease of IgE in patients with rheumatoid arthritis," because Hunder's statement implies that RA treatments directed specifically to auto-reactive (self-reactive) immune components to self-antigens could be implemented such that the general immune response (*i.e.*, total IgE levels) would remain unaffected.

As noted in Dr. Kim's Declaration, one of ordinary skill in the art would not interpret Hunder to explicitly or inherently teach that "[t]here is an increase in IgE in patients with rheumatoid arthritis" and that "[t]reatment of rheumatoid arthritis would result in the decrease of IgE in patients with rheumatoid arthritis" (as stated by the Examiner) for the following reasons: (1) Hunder states that there is no correlation between the severity of RA and IgE concentration (serum levels and synovial fluid); (2) Hunder does not report in Table

1 a statistically significant difference between the serum IgE levels of healthy patients and RA patients; (3) the serum IgE values for normal patients were derived from a previous study and may not be amenable to valid statistical analysis; (4) Hunder does not exclude the likely possibility that the lower serum IgE levels in DJD patients compared to RA patients were the result of or caused by the DJD disease state; and (5) Hunder implies that RA therapies targeting specific auto-reactive immune components against self-antigens may not affect total IgE levels.

As noted in Dr. Kim's Declaration, the general consensus in the scientific community at the time of filing of the present application was that a role for IgE antibodies in RA pathology was at most negligible or non-existent. Marcolongo, R. and Marsili, C. Z *Immun.-Forsch. Bd. 148:S* 285-290 (1975) (Exhibit E) ("Marcolongo") supports the notion that the treatment of rheumatoid arthritis would not necessarily result in the reduction of IgE production. For example, Marcolongo states, "[n]o correlation of . . . IgE values . . . with the activity and the duration of the rheumatoid arthritis was observed." See abstract of Marcolongo at page 285. Additionally, Marcolongo suggests that "the role and the importance of . . . IgE immunoglobulins may be excluded or considered to be negligible in . . . immunological response related to rheumatoid arthritis." See Marcolongo at page 288.

As further stated in Dr. Kim's Declaration, Peskett, S., Platts-Mills, T., Ansell, B., and Stearnes, G. *J. Rheumatol.* 8: 321-324 (1981) (enclosed herein as Exhibit F) ("Peskett") directly contradicts the Examiner's interpretation of Hunder regarding RA and total IgE levels. Peskett examined total IgE levels and pollen specific IgE in the sera of patients with adult RA and states in the abstract that "[t]he incidence of IgG and IgE antibodies to pollen

appeared to be low and the ***geometric mean total IgE was low***" in this patient population compared to those of a control group. *See abstract of Peskett (emphasis added).*

As further stated in Dr. Kim's Declaration, O'Driscoll, B., Milburn, H., Kemeny, D., Cochrane, G., and Panayi, G. *Clinical Allergy* 15: 547-553 (1985) (enclosed herein as Exhibit G) ("O'Driscoll") directly addresses the studies of Peskett and Hunder. O'Driscoll reports that they "[d]id not find an elevated serum level of IgE in RA patients compared with controls" and that their results "[w]ere similar to those of Peskett *et al.* who found that ***total serum IgE in adults with RA was similar to (but slightly lower than) that of normal controls.***" *See O'Driscoll at page 552, paragraph 5 (emphasis added).* O'Driscoll states that the findings of the Hunder study were flawed, because the authors of Hunder "[u]sed controls which were not matched for age and sex (it has subsequently been shown that serum IgE levels diminish with advancing age, especially above the age of 65 years) [18]."

See O'Driscoll at page 552, paragraph 5. O'Driscoll further elaborates on the flaws of the Hunder study in the following statement:

The high mean IgE among the RA patients was largely attributable to a small number of patients with an extremely high serum IgE. The median serum IgE was not reported... and as serum IgE values are not normally distributed, the median value is probably more important than the mean.

See O'Driscoll at page 552, paragraph 5.

In summary, the general consensus in the scientific community at the time of filing of the present application was that a role for IgE antibodies in RA pathology was at most negligible or non-existent. Marcolongo, O'Driscoll, and Peskett all confirm that there is no correlation between serum IgE levels and RA, and O'Driscoll indicates that the Hunder

study was flawed in both selection of controls and in the data analysis of serum IgE values in the various cohorts.

Thus, no relationship between the treatment of rheumatoid arthritis and the reduction of IgE production has been established by the Examiner. Additionally, no relationship between the oral treatment of rheumatoid arthritis with an extract of *Actinidia arguta* and the reduction of IgE production has been established by the Examiner. Thus, Motohashi in view of Hunder does not inherently anticipate the present invention.

In view of the above, it is respectfully submitted that Motohashi does not describe each and every element of claim 146 either expressly or inherently. Therefore, claim 146, and any claim dependent on claim 146, is not anticipated by Motohashi.

In view of the above, it is respectfully requested that the rejection of claims 146, 150, 168-169, 233, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

C. Second Rejection Under 35 U.S.C. § 102(b)

Claims 147, 150, 168-169, 233, 237, 241 and 242 are rejected under 35 U.S.C. § 102(b) as being anticipated by Motohashi in view of Myers *et al. Arthritis & Rheumatism* 43(12):2687-2693 (2000) ("Myers"). Applicants respectfully traverse this rejection.

I. Declaration by Sunyoung Kim Under 37 C.F.R. § 1.132

The Applicants' direct the Examiner to the Declaration of Sunyoung Kim, D. Phil., under 37 C.F.R. § 1.132 filed concurrently with the Reply. In this Declaration, Dr. Kim explains in detail why one of ordinary skill in the art at the time this application was filed would not have viewed Motohashi combined with Myers to teach the treatment of rheumatoid arthritis by decreasing the serum level of IgG1 and increasing the serum level of

IgG2a in a mammal in need thereof. For the reasons provided in the Declaration of Dr. Kim and those listed below, it is respectfully requested that the rejection of pending Claims 147, 150, 168-169, 233, 237, 241 and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

2. *The Pending Claims Are Not Expressly or Inherently Anticipated by Motohashi*

The present claims are not anticipated by Motohashi because the reference does not mention decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof by orally administering an extract of *Actinidia arguta*. First, Motohashi does not expressly mention decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof. The reference also does not indicate that by treating humans afflicted with any of the listed indications with an extract of *Actinidia arguta*, serum IgG1 levels would be reduced and serum IgG2a levels would be increased in humans in need thereof. In fact, the reference does not mention any relationship between serum IgG1 and IgG2a levels and the treatment of any indication. Therefore, the reference does not teach that the humans were in need of serum IgG1 level decreases and serum IgG2a level increases. Thus, Motohashi does not expressly anticipate the present claims.

Moreover, Motohashi does not inherently disclose decreasing serum IgG1 levels or increasing serum IgG2a levels in a mammal in need thereof. The Examiner has not established that the reference necessarily includes the claimed limitation "wherein said [Actinidia arguta] extract is provided in an amount sufficient to decrease the serum level of IgG1 and increase the serum level of IgG2a in said mammal." The Examiner has not shown

that an oral extract of *Actinidia arguta* administered to humans for the treatment of any of the listed indications would necessarily result in a decrease in serum IgG1 levels and an increase in serum IgG2a levels in said mammal. The Examiner has attempted to establish a direct relationship between serum IgG1 and IgG2a levels and RA by referencing Myers *et al.* Specifically, the Examiner asserts that "Myers *et al.* is solely used to show treatment of arthritis would result in the decrease of IgG1 and increase of IgG2a in patients with arthritis." See Office Action at page 7. Applicants respectfully disagree and submit that the Examiner has mischaracterized Myers.

Myers made use of a murine model system involving mice susceptible to collagen-induced arthritis (CIA) to examine the roles of COX-1 and COX-2 in the development of arthritis. Specifically, Myers *et al.* reports the vaccination of wild-type (WT), COX-1 deficient (-/-) and COX-2-/- mice with collagen II (CII) so that the mice would develop auto-reactive (self-reactive) antibodies against self-CII. The Examiner quotes the following from Myers as support for her argument:

Compared with wild-type controls, COX-1-/- mice exhibited a slight increase in IgG2a antibody production and a slight decrease in IgG1 antibodies. Conversely, COX-2-/- mice exhibited significantly depressed levels of both IgG1 and IgG2 antibodies (Table 1).

See Myers at page 2690.

The Examiner's statement that Myers shows that treatment of arthritis would result in the decrease of IgG1 and increase of IgG2a in patients with arthritis is not supported by the above quotation, and Dr. Kim's Declaration notes that the above quotation was used out of context and misinterpreted by the Examiner. We respectfully request that the Examiner

individually address the Applicants' arguments below. As detailed in *Section I.A.*, it is incumbent upon the Examiner to validate a 35 U.S.C. § 102(b) anticipation rejection by providing a reference that describes each and every element of the claim(s) either expressly or inherently. Motohashi in view of Myers does not satisfy these criteria for the following reasons.

a. Myers Does Not Disclose Methods of RA Treatment

Myers makes no mention of treating arthritis in patients or in the mice used in the study, nor does Myers report the testing of any therapeutics in the mice used in the study. Rather, Myers examined whether or not COX-1 and COX-2 are genetically required for mice to develop CIA. Therefore, the disclosure of Meyers does not support the Examiner's statement that Meyers shows "*treatment of arthritis* would result in the decrease of IgG1 and increase of IgG2a in patients with arthritis."

b. Meyers Does Not Enable One of Ordinary Skill in the Art to Predict the Effects of RA Treatment on Serum IgG1 and IgG2a Levels

Dr. Kim's Declaration points out that the experimental results of Myers are in no way relevant to a clinical setting, because Myers compared the development of CIA among the limited experimental cohorts of WT, COX-1-/ and COX-2-/ mice, all of which were given the arthritis-inducing CII vaccine. Given that Table 1 and all data disclosed by Myers lack the negative control group of WT mice having not received the CII vaccination (i.e., non-arthritis control mice), the only correlations reported in Myers were between the CII vaccinated WT (arthritic) control cohort and either the CII vaccinated COX-1-/ or the CII vaccinated COX-2-/ experimental cohorts. Since Myers does not disclose data for a non-

arthritic WT control group, Myers does not enable one of ordinary skill in the art to predict differences in the antibody levels between arthritic and non-arthritic control mice, much less between animals in a RA disease state and a non-disease state. While the mice of the COX-2/- cohort were impaired in their ability to develop RA, this cohort does not cure the negative control deficiency of Myers, because one of ordinary skill in the art would expect, at most, the COX-2 deficiency alone to alter the global immune response as well as global levels of antibody production. As Dr. Kim notes in his Declaration, one of ordinary skill in the art could not predict, based on the disclosure of Myers (and due to the lack of the appropriate negative control cohort), how RA treatment would affect serum IgG1 and IgG2a levels in either the murine model system disclosed by Myers or in a clinical setting. Thus, Motohashi in view of Myers does not anticipate the present claims.

c. The Disclosure of Myers is Limited to anti-CII Specific Antibodies

The objective of Myers was to determine the effects of COX-1 and COX-2 gene deletion on the development of CIA rather than the treatment of CIA in a clinical setting. As mentioned above, this was accomplished by attempting to induce an arthritic disease state in WT, COX-1/-, and COX-2/- mice through the immunization of the mice against CII, such that the mice develop auto-reactive (self-reactive) antibodies to self-CII. The immune response to self-CII, and hence the development of arthritis or lack thereof, was assessed by measuring anti-CII specific antibodies (IgG, IgG1, and IgG2) rather than total IgG, IgG1, or IgG2 antibody levels. As stated in Dr. Kim's Declaration, Myers does not provide any data regarding non-CII specific antibody levels, much less total IgG1 or IgG2a antibody levels. Therefore, Dr. Kim concludes in his Declaration that Myers does not

enable one of ordinary skill in the art to predict changes in non-CII specific antibody levels resulting from COX-1 and COX-2 gene deletion. Since the claims of the present invention are not limited to altering serum levels of anti-CII specific antibodies, Motohashi in view of Myers does not anticipate the present claims.

d. The Examiner Confuses Cause and Effect in Interpreting the Relationship Between the COX-2 Defect and anti-CII Antibody Levels of COX-2-/- Mice

The Examiner's statement that "[a] major factor in the inhibition of CIA in COX-2-/- mice is the inability of these mice to produce antibodies to CII" is inaccurate for the reasons stated below. See page 7 of the Office Action. As stated in Dr. Kim's Declaration, the accurate interpretation of the results disclosed by Myers is that "a major factor in the inhibition of CIA in COX-2-/- mice is the inability of these mice to respond to the CII antigenic vaccine stimulus as evidenced by diminished anti-CII specific antibody production." Myers teaches that COX-2-/- mice had a significantly lower incidence of arthritis and exhibited two defects accounting for the impaired ability of the mice to develop CIA: "[a] reduced immune response to CII *demonstrated by* a markedly reduced antibody titer, and an 'inflammatory' defect *reflected by* the inability to passively transfer arthritis to COX-2-/- mice." See abstract of Myers at page 2687 (emphasis added).

As stated in Dr. Kim's Declaration, Myers discloses that COX-2-/- mice were impaired in their development of arthritis, because the COX-2 deficiency prevented the mice from reacting to the trigger for developing arthritis, whereby the trigger is the immunization of the animal against CII such that the animal develops an auto-reactive (self-reactive) immune response against self-CII. Diminished anti-CII specific antibodies are merely the

result of the inability of COX-2-/- mice to respond to the RA disease trigger of CII vaccination. In other words, COX-2-/- deficiency was the "cause" that resulted in a reduced immune response to CII as witnessed by the "effect" or "readout" of reduced anti-CII specific antibodies. The emphasized phrases "*demonstrated by*" and "*reflected by*" in the above quotation clearly reflect the "effect" relationship of reduced anti-CII specific antibody production to the COX-2-/- immune/inflammatory defect. In this proper context of cause and effect, therefore, Myers shows that the decreased levels of anti-CII specific IgG1 and IgG2 in COX-2-/- mice are a readout for the impaired ability to *develop* arthritis following CII vaccination. Dr. Kim explains in his Declaration that the disclosure of Myers does not support the notion that COX-2 inhibition could be a means of *treating* RA, because the COX-2 deficiency operated at the level of *preventing the induction of the RA disease state* (i.e., at the level of CII vaccination response).

Thus, the treatment of RA by decreasing the level of IgG1 and increasing the level of IgG2a is neither suggested nor implied by Myers. Rather, Myers at most indicates that the inhibition of COX-2 could be a means of *preventing* RA. Given that COX-2-/- mice were inhibited at the level of RA acquisition, one of ordinary skill in the art could not predict the effects of COX-2 inhibition on the treatment of RA, much less the effects of COX-2 inhibition on serum antibody levels in an active RA disease state. In conclusion, Motohashi in view of Myers does not anticipate the present claims.

e. *The Decreased IgG1 and Increased IgG2a Levels in Arthritic COX-1-/- Mice is Defined in Relation to Arthritic Control Mice and is Irrelevant to RA Treatment*

Myers discloses that the COX-1-/- cohort developed arthritis as evidenced by the presence of self-reactive CII-specific antibodies. Table 1 indicates that a significant difference in IgG1 and IgG2a levels was observed only between CII vaccinated COX-2-/- mice and CII vaccinated WT (arthritic) mice, but not between CII vaccinated (arthritic) COX-1-/- mice and CII vaccinated (arthritic) WT mice. As stated in Dr. Kim's Declaration, the statement "[c]ompared with wild-type controls, COX-1-/- mice exhibited a slight increase in IgG2a antibody production and a slight decrease in IgG1 antibodies" has no validity by scientifically accepted statistical standards and should be interpreted as "compared with wild-type controls, there was no correlation between COX-1-/- deficiency and CII-specific IgG1 or IgG2a antibody levels." See Section I.B.2. Even if the antibody levels were significantly different between CII vaccinated COX-1-/- (arthritic) mice and CII vaccinated (arthritic) WT mice, which they were not, both of these cohorts were arthritic and did not receive anti-arthritis therapy. Therefore the disclosure of Myers that "[c]ompared with wild-type controls, COX-1-/- mice exhibited a slight increase in IgG2a antibody production and a slight decrease in IgG1 antibodies" does not support the Examiner's argument that Myers shows "[t]reatment of arthritis would result in the decrease of IgG1 and increase of IgG2a in patients with arthritis." For the Examiner's statement to be valid, a comparison between arthritic (CII vaccinated WT or COX-1-/-) mice and non-arthritic (non-CII vaccinated WT) mice would need to have been disclosed by Myers, which was not the

case (*see* Section I.C.2.b.). Thus, Motohashi in view of Myers does not anticipate the present claims.

h. Summary

For the reasons outlined above, no relationship between the treatment of arthritis, let alone rheumatoid arthritis, and decreases in serum IgG1 levels and increases in serum IgG2a levels has been established. Additionally, no relationship between the oral treatment of rheumatoid arthritis with an extract of *Actinidia arguta* and decreases in serum IgG1 levels and increases in serum IgG2a levels has been established by the Examiner. Thus, Motohashi does not inherently anticipate the present invention.

In view of the above, it is respectfully submitted that Motohashi does not describe each and every element of claim 147 either expressly or inherently. Therefore, claim 147, and any claim dependent on claim 147, is not anticipated by Motohashi.

In view of the above, it is respectfully requested that the rejection of claims 147, 150, 168-169, 233, 237, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

D. Third Rejection Under 35 U.S.C. § 102(b)

Claims 148, 150, 158, 168-169, 233, 237, 241, and 242 are rejected under 35 U.S.C. § 102(b) as being anticipated by Motohashi in view of Yudoh *et al.* *Arthritis & Rheumatism* 43(3):617-627 (2000) ("Yudoh"). Applicants respectfully traverse this rejection.

I. Declaration by Sunyoung Kim Under 37 C.F.R. § 1.132

The Applicants' direct the Examiner to the Declaration of Sunyoung Kim, D. Phil., filed under 37 C.F.R. § 1.132 filed concurrently with the Reply. In this Declaration, Dr. Kim explains in detail why one of ordinary skill in the art at the time this application was

filed would not have been motivated by Motohashi in view of Yudoh to treat rheumatoid arthritis by simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof. Based upon the arguments disclosed in the Declaration of Dr. Kim and those listed below, it is respectfully requested that the rejection of pending Claims 148, 150, 158, 168-169, 233, 237, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

2. *The Pending Claims Are Not Expressly or Inherently Anticipated by Motohashi*

The present claims are not anticipated by Motohashi because the reference does not disclose simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof by orally administering an extract of *Actinidia arguta*. First, Motohashi does not expressly mention simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof. The reference also does not indicate that by treating humans afflicted with any of the listed indications with an extract of *Actinidia arguta*, serum Th2 cytokines would be reduced and serum Th1 cytokines would be increased simultaneously in humans in need thereof. In fact, the reference does not mention any relationship between serum Th2 and Th1 cytokines and the treatment of any indication. Therefore, the reference does not teach that the humans were in need of serum Th1 cytokine increases and serum Th2 cytokine decreases. Thus, Motohashi does not anticipate the present claims.

Moreover, Motohashi does not inherently describe simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof. The Examiner has not established that the reference necessarily includes the claimed limitation

"wherein said [*Actinidia arguta*] extract is provided in an amount sufficient to simultaneously decrease serum Th2 cytokines and increase Th1 cytokines in said mammal." Specifically, the Examiner has not shown that an oral extract of *Actinidia arguta* administered to humans for the treatment of any of the listed indications would *necessarily result in the simultaneous decrease Th2 serum cytokines and increase Th1 serum cytokines in said mammal*. While the Examiner has attempted to establish a direct relationship between serum Th1 and Th2 cytokines and rheumatoid arthritis ("RA") by referencing Yudoh, the Examiner has actually mischaracterized Yudoh. The Examiner characterizes Yudoh as follows:

Yudoh et al. teaches in rheumatoid arthritis, reduced expression of the CD4+ T cell subset producing IL-10 but not IL-2 and IL-4 may be responsible for the dominance of Th1 over Th2 cells at sites of inflamed synovium and in the peripheral blood....Yudoh et al. is solely used to show treatment of arthritis would result in the decrease of TH2 and increase of TH1 in patients with rheumatoid arthritis.

See Office Action at pages 7-8. Applicants respectfully disagree. The Examiner has misinterpreted the teachings of Yudoh, and Yudoh does not anticipate the present claims for the reasons stated below.

Yudoh states that "[i]n RA, reduced expression of the CD4+ T cell subset producing IL-10 but not IL-2 and IL-4 may be responsible for the dominance of Th1 over Th2 cells at sites of inflamed synovium and in the peripheral blood." *See* Yudoh abstract at page 617. In other words, reduced expression of T regulatory type 1 (Tr1) cells in RA patients may result in increased Th1 cells and decreased Th2 cells in the blood and sites of disease. Yudoh concludes that "[d]ecreases in this type of CD4+ T cell subset may induce the down-

regulation of T cell tolerance and exacerbate the inflammatory process in RA." *See* Yudoh abstract at page 617. In other words, reduced expression of Tr1 cells is associated with increased Th1 cells and/or decreased Th2 cells according to Yudoh, and reduced expression of Tr1 cells may worsen the inflammatory process in RA. As stated in Dr. Kim's Declaration, one of ordinary skill in the art at most would be motivated by the teachings of Yudoh to treat RA by decreasing a Th1 response or increasing a Th2 response. However, the present application claims a method for simultaneously increasing Th1 serum cytokines and decreasing Th2 serum cytokines. Yudoh reiterates the notion above by stating that their findings "[s]uggest that decreased expression of CD4+ T cell subset producing IL-10 but not IL-4 and IL-2 may be responsible for the dominance of Th1 cells over Th2 cells in the peripheral blood and in synovial tissue of patients with RA." *See* abstract of Yudoh at page 624. This statement suggests, at most, that rheumatoid arthritis treatment would require a reduction in serum Th1 cytokines and an increase in serum Th2 cytokines, not an increase in serum Th1 cytokines and a reduction in serum Th2 cytokines as is recited in the pending claims.

Furthermore, Yudoh states that "[n]o significant correlations were observed between the Th1:Th2 ratio in the peripheral blood and disease severity (disease activity score and parameters of inflammation) in RA patients." *See* Yudoh at page 624. This statement alone implies that the treatment of arthritis may not necessarily result in changes in serum Th1 and Th2 cytokines, much less the simultaneous increase of serum Th1 cytokines and decrease of serum Th2 cytokines.

As stated above, the Examiner has misinterpreted the teachings of Yudoh. Yudoh suggests a link between RA and increased serum Th1 cytokines and decreased serum Th2 cytokines. Therefore one of ordinary skill in the art would at most be motivated to treat rheumatoid arthritis by reducing serum Th1 cytokines and/or increasing serum Th2 cytokines. The present application, however, claims a method for simultaneously increasing serum Th1 cytokines and decreasing serum Th2 cytokines. As stated in Dr. Kim's Declaration, further support for the link between RA disease and increased serum Th1 cytokines and decreased serum Th2 cytokines is disclosed in Schulze-Koops, H. and Kalden, *J. Best Practice & Research Clinical Rheumatology* 15: 677-691 (2001) (enclosed herein as Exhibit J) ("Schulze-Koops") and Hermann, J., Walmsley, M., Brennan, F. *Springer Semin. Immunopathol.* 20: 275-288 (1998) (enclosed herein as Exhibit K) ("Hermann"). Schulze-Koops, which is a review article summarizing the state of research at the time of filing regarding the role of Th1 and Th2 cytokines in RA, concludes in the following statement that RA is a disease driven by increased Th1 cellular activation and that shifting the Th1/Th2 balance towards increased Th2 cellular activation might be effective for treating RA:

In RA, convincing arguments, both clinical and experimental, have been provided to suggest that autoimmune rheumatoid inflammation is also driven by activated Th1 effectors without sufficient Th2 generation to downregulate inflammation. Furthermore, recent data suggest that *several treatment modalities currently employed in RA, exert their immunomodulatory effect at least in part by inhibiting Th1 cell activation and/or differentiation and by favouring Th2 differentiation, thereby shifting the Th1/Th2 balance towards the Th2 direction. Thus selective manipulation of Th cell differentiation to induce Th2 effectors might be a successful*

approach for interrupting ongoing and established Th1-driven chronic autoimmune diseases such as RA.

See Schulze-Koops at page 688 (emphasis added).

Schulze-Koops further states that IL-4, which is a Th2 cytokine, is "[s]uitable for ameliorating signs and symptoms of chronic arthritis." *See Schulze-Koops at page 681.* These teachings are in direct contrast to the Examiner's interpretation of Yudoh and indicate that treatment of RA would not necessarily result in a decrease in Th2 serum cytokines.

Similar to Schulze-Koops, Hermann is a review article summarizing the state of research at the time of filing regarding cytokine therapy in rheumatoid arthritis. Hermann further suggests in the following statement that increasing Th2-derived cytokines (i.e., IL-4) may be useful in treating RA:

This and other evidence suggests that CD4+ Th2-derived cytokines are not abundant in RA joints, and that CD4+ Th1 cells predominate in this site. It is possible that the lack of IL-4 producing CD4+ Th2 cells contributes to the pathogenesis of RA, and this has led to suggestions that IL-4 may be a useful therapeutic agent.

See Hermann at page 282.

Based on the teachings of Yudoh, Schulze-Koops, and Hermann, one of ordinary skill in the art would expect that treatment of RA would, at most, result in the increase of Th2 cytokines and the decrease of Th1 cytokines in RA patients. Thus, one of ordinary skill in the art would be motivated, at most, to treat rheumatoid arthritis by reducing serum Th1 cytokines and/or increasing serum Th2 cytokines. The present application, however, claims a method for simultaneously increasing serum Th1 cytokines and decreasing serum Th2 cytokines. Thus, no relationship between the treatment of rheumatoid arthritis and

simultaneous decreases in serum Th2 cytokines and increases in serum Th1 cytokines has been established by the Examiner. Additionally, no relationship between the oral treatment of rheumatoid arthritis with an extract of *Actinidia arguta* and simultaneous decreases in serum Th2 cytokines and increases in serum Th1 cytokines has been established by the Examiner. Thus, Motohashi does not inherently anticipate the present invention.

In view of the above, it is respectfully submitted that Motohashi does not describe each and every element of claim 148 either expressly or inherently. Therefore, claim 148, and any claim dependent on claim 148, is not anticipated by Motohashi.

In view of the above, it is respectfully requested that the rejection of claims 148, 150, 158, 168-169, 233, 237, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

E. Fourth Rejection Under 35 U.S.C. § 102(b)

Claims 176, 180, 197-198, 233, 237, 241, and 242 are rejected under 35 U.S.C. § 102(b) as being anticipated by Motohashi in view of Permin *et al.* *Allergy* 36(6):435-436 (1981) ("Permin"). Applicants respectfully traverse this rejection.

The present claims are not anticipated by Motohashi because the reference does not disclose decreasing histamine release in a mammal in need thereof by orally administering an extract of *Actinidia arguta*. First, Motohashi does not expressly describe decreasing histamine release in a mammal in need thereof. The reference also does not indicate that by treating humans afflicted with any of the listed indications with an extract of *Actinidia arguta*, histamine release would be decreased in humans in need thereof. In fact, the reference does not disclose any relationship between histamine release and the treatment of

any indication. Therefore, the reference does not teach that the humans were in need of histamine release reduction. Thus, Motohashi does not anticipate the present claims.

Moreover, Motohashi does not inherently describe decreasing histamine release in a mammal in need thereof. The Examiner has not established that the reference necessarily includes the claimed limitation "administering an extract of *Actinidia arguta* to said mammal in an amount sufficient to decrease histamine release in said mammal." The Examiner has not shown that an oral extract of *Actinidia arguta* administered to humans for the treatment of any of the listed indications would *necessarily result in a decrease in histamine release in said mammal*. The Examiner has attempted to establish a direct relationship between histamine release and rheumatoid arthritis ("RA") by referencing Permin. The Examiner asserts as follows:

Permin et al. is solely used to show a role of histamine in rheumatoid arthritis is also supported by the findings of clinical improvement during treatment with H₁ and H₂ antihistamines in six of 12 patients with rheumatoid arthritis in active phase, whereas four showed definite deterioration. Hence, treatment of rheumatoid arthritis would result in the decrease of histamine in patients with rheumatoid arthritis.

See Office Action at page 8. Applicants respectfully disagree.

The Examiner has completely glossed over the fact that Permin admitted to four of the twelve patients with rheumatoid arthritis in active phase showing "definite deterioration" after being administered antihistamines, **which means that the RA symptoms worsened in these patients.** Additionally, two of those same twelve patients did not show clinical improvement with antihistamine treatment at all. Given that only six out of twelve patients beneficially responded to antihistamine treatment, the probability of a beneficial response to

antihistamine therapy was reported to be no greater than 50% random chance. These facts alone suggest that the treatment of arthritis may not necessarily result in the reduction of histamine release. Additionally, it is known in the art that RA patients display significantly lower levels of histamine in circulation as compared with healthy individuals. *See Adlesic, M. et al., Scand. J. Immunol. 65:530-537 (2007)* (enclosed herein as Exhibit L) ("Adlesic").

Thus, no relationship between the treatment of rheumatoid arthritis and histamine release reduction has been established. Additionally, no relationship between the oral treatment of rheumatoid arthritis with an extract of *Actinidia arguta* and histamine release reduction has been established by the Examiner. Thus, Motohashi does not inherently anticipate the present invention.

In view of the above, it is respectfully submitted that Motohashi does not describe each and every element of claim 176 either expressly or inherently. Therefore, claim 176, and any claim dependent on claim 176, is not anticipated by Motohashi.

In view of the above, it is respectfully requested that the rejection of claims 176, 180, 197-198, 233, 237, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

F. Fifth Rejection Under 35 U.S.C. § 102(b)

Claims 177, 197-198, 233, 237, 241, and 242 are rejected under 35 U.S.C. § 102(b) as being anticipated by Motohashi in view of McGonagle *et al. Arthritis & Rheumatism* 42(8):1706-1711 (1999) ("McGonagle"). Applicants respectfully traverse this rejection.

The present claims are not anticipated by Motohashi because the reference does not disclose decreasing edema in a mammal in need thereof by orally administering an extract of *Actinidia arguta*. First, Motohashi does not expressly describe decreasing edema in a

mammal in need thereof. The reference also does not indicate that by treating humans afflicted with any of the listed indications with an extract of *Actinidia arguta*, edema would be decreased in humans in need thereof. In fact, the reference does not mention any relationship between edema and the treatment of any indication. Therefore, the reference does not teach that the humans were in need of edema reduction. Thus, Motohashi does not anticipate the present claims.

Moreover, Motohashi does not inherently teach decreasing edema in a mammal in need thereof. The Examiner has not established that the reference necessarily includes the claimed limitation "administering an extract of *Actinidia arguta* to said mammal in an amount sufficient to decrease edema in said mammal." The Examiner has not shown that an oral extract of *Actinidia arguta* administered to humans for the treatment of any of the listed indications would *necessarily decrease edema in said mammal*. The Examiner has attempted to establish a direct relationship between edema and rheumatoid arthritis ("RA") by referencing McGonagle. The Examiner asserts as follows:

McGonagle et al. is solely used to show metacarpophalangeal joint bone edema is present in the majority of patients with RA at presentation, but is seen only occasionally in normal control subjects.... treatment of rheumatoid arthritis would result in the decrease of edema in patients with rheumatoid arthritis.

See Office Action at page 9. Applicants respectfully disagree.

As stated above, if the prior art does not necessarily function in accordance with, or does not include, the claimed limitations, it does not anticipate. *Mehl/Biophile International Corp. v. Milgram, 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999).*

McGonagle observed that only 68% of RA patients exhibited bone edema. 32% of the RA patients did not exhibit bone edema. *See McGonagle Abstract.* Thus, bone edema is not necessarily associated with RA. Additionally, McGonagle does not disclose any RA treatment method, let alone an RA treatment method that will necessarily reduce edema. Thus, a patient being treated for RA might not have edema and, therefore, would not experience a reduction in edema as is required by the claims. These facts alone suggest that the treatment of arthritis may not necessarily result in the reduction of edema.

Thus, no relationship between the treatment of rheumatoid arthritis and edema reduction has been established. Additionally, no relationship between the oral treatment of rheumatoid arthritis with an extract of *Actinidia arguta* and edema reduction has been established by the Examiner. Thus, Motohashi does not inherently anticipate the present invention.

In view of the above, it is respectfully submitted that Motohashi does not describe each and every element of claim 177 either expressly or inherently. Therefore, claim 177, and any claim dependent on claim 177, is not anticipated by Motohashi.

In view of the above, it is respectfully requested that the rejection of claims 177, 197-198, 233, 237, 241, and 242 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

G. First Rejection Under 35 U.S.C. § 103(a)

Claims 155-157, 170-171, 173, 185-187, 199-200, 239, and 243-244 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Motohashi as applied to claims 146-148, 150, 158, 168-169, 176-177, 180, 197-198, 233, 237, 241, and 242. Applicants respectfully traverse this rejection.

1. Elements of a Prima Facie Case of Obviousness

In order to establish a *prima facie* case of obviousness, (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the prior art reference (or references when combined) must teach or suggest all the claim limitations; and (3) there must be a reasonable expectation of success. MPEP § 2143.

2. Motohashi Does Not Expressly or Inherently Teach or Suggest all the Claim Limitations of the Pending Claims

As discussed above, Motohashi does not expressly or inherently teach or suggest all the claim limitations of the pending claims. In particular, the cited reference does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release or decreasing edema via the oral administration of an extract of *Actinidia arguta*.

3. Motohashi in View of Myers Teaches Away from the Pending Claims

The Examiner alleges that Motohashi in view of Myers anticipates the present invention's claimed method of decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof. Applicants submit that Motohashi in view of Myers in fact *teaches away* from the claimed method of decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof. Given that the COX-2-/ mice were impaired in developing arthritis, no meaningful information was provided (nor claimed) by the authors of Myers relating to the effects of arthritis treatment on anti-CII

specific IgG1 and IgG2 antibody levels or total/global IgG1 and IgG2 antibody levels in COX-2/- mice. Since the passive transfer of arthritis was impaired in the COX2-/- mice, the only pertinent information that can be taken from the data regarding the COX-2/- cohort is that COX-2 was required for the development of CIA. Therefore, the Examiner's quotation that "COX-2/- mice exhibited significantly depressed levels of both IgG1 and IgG2 antibodies," which was used to build the Examiner's argument for the rejection under 35 U.S.C. § 102(b), is taken out of context and is irrelevant to both arthritis treatment and the present invention. *See* Office Action at page 7. Moreover, Myers teaches away from the Applicant's claims, because one of ordinary skill in the art would be motivated by the disclosure of Myers to prevent RA by directly inhibiting COX-2.

Considering, solely for the sake of argument, that one of ordinary skill in the art would interpret decreased anti-CII specific IgG1 and IgG2a antibody production in COX-2/- non-arthritic mice as the causal mechanism for the reduced incidence of RA, which it is not, Myers would nevertheless teach away from the claims of the present invention. Along this line of reasoning, one of skill in the art would be motivated by Myers to *decrease IgG2a levels*, while the claims of the present invention relate to a method for decreasing the serum level of IgG1 and *increasing the serum level of IgG2a*. Thus, Motohashi in view of Myers teaches away from the claimed method of decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof.

As stated in Dr. Kim's Declaration, the art at the time of filing teaches away from the Applicants' strategy of decreasing the serum level of IgG1 and increasing the serum level of IgG2a and at most would motivate one of ordinary skill in the art to decrease the serum level

of IgG1 and *decrease the serum level of IgG2a* for the purpose of treating RA. Yamaki, K., Uchida, H., Harada, Y., Li, X., Yanagisawa, R., Takano, H., Hayashi, H., Taneda, S., Mori, Y., and Yoshino, S. *J. Pharm. Pharmacol.* 55: 1661-1666 (2003) (enclosed herein as Exhibit H) ("Yamaki") states the following:

The results showed that treatment with MTX was followed by decreases in OVA-specific IgG and proliferation of spleen cells to the antigen. *The anti-rheumatic drug inhibited both anti-OVA IgG2a and IgG1 production*, although the inhibitory effect of MTX on the antigen-specific IgG2a production appeared to be greater than that on IgG1 production.

See Abstract of Yamaki at page 1661 (emphasis added).

Mukherjee, P., Wu, B., Mayton, L., Kim, S-H, Robbins, P., and Wooley, P. *Ann. Rheum. Dis.* 62: 707-714 (2003) (enclosed herein as Exhibit I) ("Mukherjee") states the following:

Results: Severity of CIA was significantly decreased in TNF-R treated animals compared with controls, 14-34 days after disease onset... Seven days after disease onset, *TNF-R treated mice had lower levels of inflammatory Th1 driven IgG2a antibodies to CIA than controls...* Conclusions: The overall influence of TNF-R gene therapy is that it *inhibits the progression of CIA mainly by suppressing the inflammatory Th1 response* rather than by stimulating a Th2 response. Therefore, periarticular TNF-R gene therapy may have excellent therapeutic potential in RA.

See Abstract of Mukherjee at page 707 (emphasis added).

Yamaki and Mukherjee, therefore, contradict the Examiner's claim, which was based on a misinterpretation of Myers, that "[t]reatment of arthritis would result in the decrease of IgG1 and *increase of IgG2a* in patients with arthritis." *See Office Action at page 7.*

4. Motohashi in View of Yudoh Teaches Away from the Pending Claims

The Examiner alleges that Motohashi in view of Yudoh anticipates the present invention's claimed method of simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof. Applicants submit that Motohashi in view of Myers in fact teaches away from the claimed method of simultaneously decreasing Th2 serum cytokines and increasing Th1 serum cytokines in a mammal in need thereof. Yudoh states that "[i]n RA, reduced expression of the CD4+ T cell subset producing IL-10 but not IL-2 and IL-4 may be responsible for the dominance of Th1 over Th2 cells at sites of inflamed synovium and in the peripheral blood." See Yudoh abstract at page 617. As stated above in Section I.D.2., Yudoh teaches that reduced expression of T regulatory type 1 (Tr1) cells in RA patients may result in increased Th1 cells and decreased Th2 cells in the blood and sites of disease. Yudoh concludes that "[d]ecreases in this type of CD4+ T cell subset may induce the down-regulation of T cell tolerance and exacerbate the inflammatory process in RA." See Yudoh abstract at page 617. In other words, reduced expression of Tr1 cells is associated with increased Th1 cells and/or decreased Th2 cells according to Yudoh, and reduced expression of Tr1 cells may worsen the inflammatory process in RA.

As stated in Dr. Kim's Declaration, one of ordinary skill in the art at most would be motivated by the teachings of Yudoh to treat RA by decreasing a Th1 response or increasing a Th2 response. However, the present application claims a method for simultaneously increasing Th1 serum cytokines and decreasing Th2 serum cytokines. Yudoh further teaches away from the present invention by stating that their findings "[s]uggest that decreased

expression of CD4+ T cell subset producing IL-10 but not IL-4 and IL-2 may be responsible for the dominance of Th1 cells over Th2 cells in the peripheral blood and in synovial tissue of patients with RA." See Yudoh abstract at page 624. One of ordinary skill in the art would interpret the previous statement to suggest that rheumatoid arthritis treatment involve a reduction in serum Th1 cytokines and an increase in serum Th2 cytokines, not an increase in serum Th1 cytokines and a reduction in serum Th2 cytokines as is recited in the pending claims.

Schulze-Koops, which is a review article summarizing the state of research at the time of filing regarding the role of Th1 and Th2 cytokines in RA, concludes in the following statement that RA is a disease driven by increased Th1 cellular activation and that shifting the Th1/Th2 balance towards increased Th2 cellular activation might be effective for treating RA:

In RA, convincing arguments, both clinical and experimental, have been provided to suggest that autoimmune rheumatoid inflammation is also driven by activated Th1 effectors without sufficient Th2 generation to downregulate inflammation. Furthermore, recent data suggest that *several treatment modalities currently employed in RA, exert their immunomodulatory effect at least in part by inhibiting Th1 cell activation and/or differentiation and by favouring Th2 differentiation, thereby shifting the Th1/Th2 balance towards the Th2 direction.* Thus selective manipulation of Th cell differentiation to induce Th2 effectors might be a successful approach for interrupting ongoing and established Th1-driven chronic autoimmune diseases such as RA.

See Schulze-Koops at page 688 (emphasis added).

Schulze-Koops clearly states that current RA treatments operate at the level of Th1 inhibition, which teaches away from the Applicants' claimed method for simultaneously

decreasing Th2 serum cytokines and increasing Th1 serum cytokines. Schulze-Koops further teaches away from the Applicants' claimed methods by stating that IL-4, which is a Th2 cytokine, is "[s]uitable for ameliorating signs and symptoms of chronic arthritis." See Schulze-Koops at page 681. Hermann, which is a review article summarizing the state of research at the time of filing regarding cytokine therapy in RA treatment, further teaches away from the claimed methods of the present application and suggests in the following statement that increasing Th2-derived cytokines (i.e., IL-4) may be useful in treating RA:

This and other evidence suggests that CD4+ Th2-derived cytokines are not abundant in RA joints, and that CD4+ Th1 cells predominate in this site. It is possible that the lack of IL-4 producing CD4+ Th2 cells contributes to the pathogenesis of RA, and this has led to suggestions that IL-4 may be a useful therapeutic agent.

See Hermann at page 282.

Based on the teachings of Yudoh, Schulze-Koops, and Hermann, one of ordinary skill in the art would expect that treatment of RA would, at most, result in the increase of Th2 cytokines and the decrease of Th1 cytokines in RA patients.

In summary, Yudoh, Schulze-Koops, and Hermann teach away from the Applicants' method of simultaneously decreasing the serum level of IgG1 and increasing the serum level of IgG2a in a mammal in need thereof. One of ordinary skill in the art would be motivated, at most, to treat rheumatoid arthritis by reducing serum Th1 cytokines and/or increasing serum Th2 cytokines.

Thus, the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully request that the rejection be reconsidered and withdrawn.

H. Second Rejection Under 35 U.S.C. § 103(a)

Claims 172, 174, 201, and 203 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Motohashi as applied to claims 146-148, 150, 155-158, 168-171, 173, 176-177, 180, 185-187, 197-200, 202, 233, 237, 239, and 241-244 in view of U.S. Patent No. 6,630,163 ("Murad"). Applicants respectfully traverse this rejection.

As discussed above, Motohashi does not expressly or inherently teach or suggest all the claim limitations of the pending claims. In particular, the cited reference does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Murad does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Accordingly, Murad fails to cure the deficiencies of Motohashi. Thus, the combination of references fails to teach or suggest all of the claim limitations of the pending claims. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully request that the rejection be reconsidered and withdrawn.

I. Third Rejection Under 35 U.S.C. § 103(a)

Claims 151-153, 159-167, 181-183, 188-196, 238, and 240 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Motohashi as applied to claims 146-148, 150,

155-158, 168-171, 173, 176-177, 180, 185-187, 197-200, 202, 233, 237, 239, and 241-244

in view of JP 02202808 A ("Tsuboi"). Applicants respectfully traverse this rejection.

As discussed above, Motohashi does not expressly or inherently teach or suggest all claim limitations of the pending claims. In particular, the cited reference does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Tsuboi does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Accordingly, Tsuboi fails to cure the deficiencies of Motohashi. The combination of references fails to teach or suggest all of the claim limitations of the pending claims. Thus, the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully request that the rejection be reconsidered and withdrawn.

J. Fourth Rejection Under 35 U.S.C. § 103(a)

Claims 154 and 184 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Motohashi and Tsuboi, as applied to claims 146-148, 150-153, 155-171, 173, 176-177, 180-183, 185-200, 202, 233, and 237-244 and in view of U.S. Publ. No. 20020054923 A1 ("Suzuki"). Applicants respectfully traverse this rejection.

As discussed above, Motohashi does not expressly or inherently teach or suggest all the claim limitations of the pending claims. In particular, the cited reference does not teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Neither Tsuboi nor Suzuki teach expressly or inherently methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, reducing histamine release, or decreasing edema via the oral administration of an extract of *Actinidia arguta*. Accordingly, Tsuboi and Suzuki fail to cure the deficiencies of Motohashi. The combination of references fails to teach or suggest all of the claim limitations of the pending claims. Thus, the Examiner has failed to make a *prima facie* case of obviousness. Applicants respectfully request that the rejection be reconsidered and withdrawn.

K. Double-Patenting Rejections

Claims 146-148, 150-174, 176, 177, 180-203, 233, and 237-244 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 130-132, 134-142, 145, 146, and 149-157 of U.S. Appl. No. 11/522,511. Applicants respectfully request that this rejection be held in abeyance until otherwise allowable claims are identified, at which time Applicants will consider filing a Terminal Disclaimer.

Claims 146-148, 150-174, 176, 177, 180-203, 233, and 237-244 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

1-30, 34-37, 42-44, 55, 58, 60, 63, 65, and 67 of U.S. Appl. No. 12/180,723. Applicants respectfully request that this rejection be held in abeyance until otherwise allowable claims are identified, at which time Applicants will consider filing a Terminal Disclaimer.

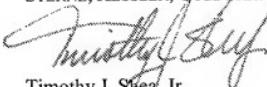
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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